Advanced Regression: Distributed non-linear lag models and other extensions

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Overview

Concepts we cover in this lecture:

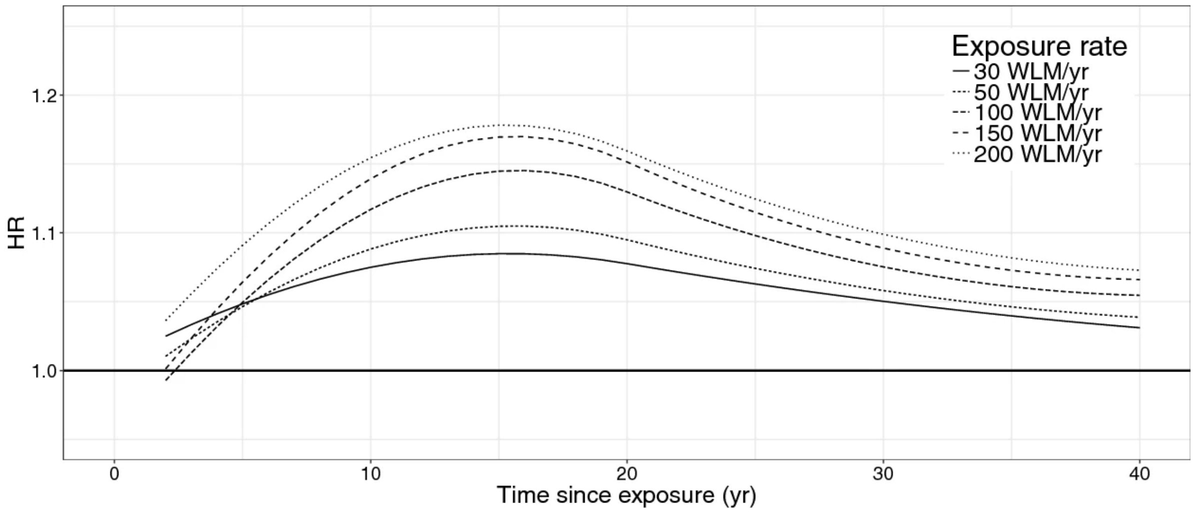
- Distributed lag non-linear models
- Cross-basis function
- Case studies

Introduction of the problem

- An exposure event is frequently associated with a risk lasting for a defined period in the future
- The risk at a given time is assumed a result of protracted exposures experienced in the past
- Examples include, drugs, carcinogens, etc.

Challenge: The risk should be modelled in terms of contributions depending oni ntensity and timing of the exposure events: bi-dimensional association (interaction).

Example 1: Lung cancer and radon exposure



Example 2: PM10 in Chicago

```r
library(dlnm)
library(ggplot2)
library(dplyr)

k <- 1:16
res_store <- list()

for (i in 1:length(k)) {
  chicagoNMMAPS$pm10_laggeg <- lag(chicagoNMMAPS$pm10, n = k[i] - 1)

  mgcv::gam(
    death ~ s(temp) +
      s(time) + s(month) + dow + pm10_laggeg,
    data = chicagoNMMAPS, family = "poisson"
  ) -> tmp

  res_store[[i]] <- list(
    est = coef(tmp)["pm10_laggeg"],
    LL = coef(tmp)["pm10_laggeg"] - 1.96 * summary(tmp)$se["pm10_laggeg"],
    UL = coef(tmp)["pm10_laggeg"] + 1.96 * summary(tmp)$se["pm10_laggeg"]
  )
}
```

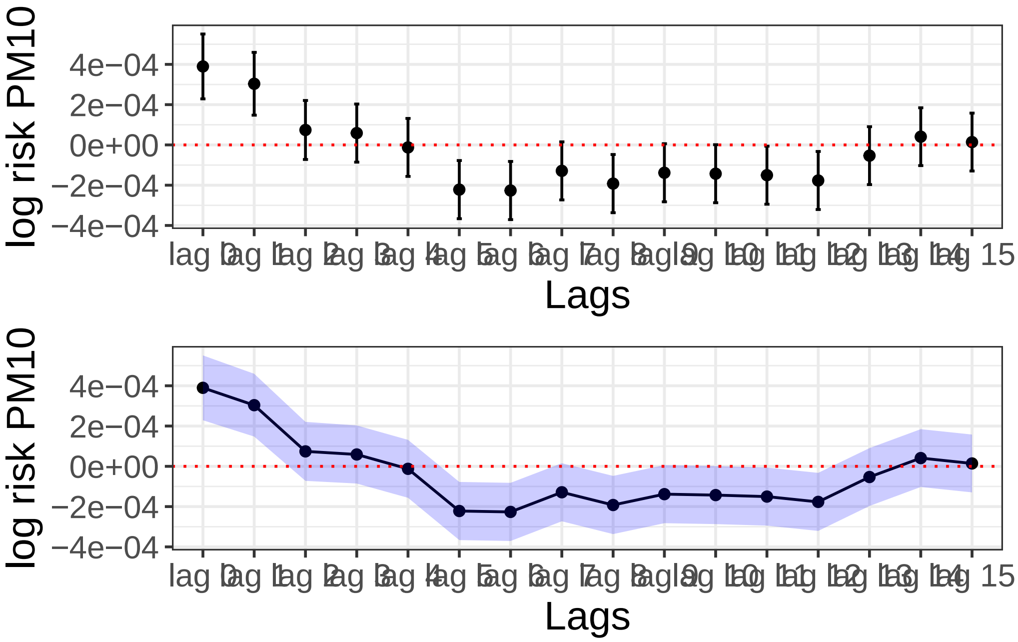
```r
lapply(res_store, unlist) %>%
  do.call(rbind, .) %>%
  as_tibble() %>%
  mutate(
    type =
      factor(paste0("lag ", 0:15),
        levels = paste0("lag ", 0:15)
      )
  ) -> plotres

ggplot(data = plotres) +
  geom_point(aes(x = type, y = est.pm10_laggeg)) +
  # geom_line(aes(x=type, y=est.pm10_laggeg, group=1), linetype = "dashed") +
  geom_errorbar(aes(x = type, ymin = LL.pm10_laggeg,
                    ymax = UL.pm10_laggeg, width = 0.1)) +
  geom_hline(yintercept = 0, col = "red", linetype = "dotted") +
  theme_bw() +
  ylab("log risk PM10") +
  xlab("Lags") -> p1


ggplot(data = plotres) +
  geom_point(aes(x = type, y = est.pm10_laggeg)) +
  geom_line(aes(x = type, y = est.pm10_laggeg, group = 1)) +
  geom_ribbon(aes(x = type, ymin = LL.pm10_laggeg,
                  ymax = UL.pm10_laggeg, group = 1),
              fill = "blue", alpha = 0.2) +
  geom_hline(yintercept = 0, col = "red", linetype = "dotted") +
  theme_bw() +
  ylab("log risk PM10") +
  xlab("Lags") -> p2
```

Example 2: PM10 in Chicago

What are the main assumptions here?

Distributed linear lag models

The unconstrained distributed lag model of order q is:



$$Y_t = \beta_0 + \beta_{10} X_t + \beta_{11} X_{t-1} + \cdots + \beta_{1q} X_{t-q} + \epsilon_t$$

- $\beta_{1\ell}$ is the effect at lag $\ell = 0, 1, \ldots q$ and ϵ_t an error term.
- The overall impact for a unit change in X is given by $\sum_{\ell=0}^{q} \beta_\ell$.

Example 2: PM10 in Chicago

```
chicagoNMMAPS$pm10_laggeg0 <- lag(chicagoNMMAPS$pm10, n = 0)
chicagoNMMAPS$pm10_laggeg1 <- lag(chicagoNMMAPS$pm10, n = 1)
chicagoNMMAPS$pm10_laggeg2 <- lag(chicagoNMMAPS$pm10, n = 2)
chicagoNMMAPS$pm10_laggeg3 <- lag(chicagoNMMAPS$pm10, n = 3)

mgcv::gam(death ~ s(temp) +
  s(time) + s(month) + dow + pm10_laggeg0 + pm10_laggeg1 + pm10_laggeg2 +
  pm10_laggeg3, data = chicagoNMMAPS, family = "poisson") %>% summary()
```

```
Family: poisson
Link function: log
```

```
Formula:
death ~ s(temp) + s(time) + s(month) + dow + pm10_laggeg0 + pm10_laggeg1 +
    pm10_laggeg2 + pm10_laggeg3

Parametric coefficients:
               Estimate Std. Error z value Pr(>|z|)
(Intercept)   4.707e+00  5.825e-03 808.083  < 2e-16 ***
dowMonday     2.898e-02  5.375e-03   5.391 7.01e-08 ***
dowTuesday    2.326e-02  5.428e-03   4.285 1.82e-05 ***
dowWednesday  5.054e-03  5.447e-03   0.928 0.353470
dowThursday   5.898e-03  5.385e-03   1.095 0.273446
dowFriday     1.294e-02  5.336e-03   2.426 0.015263 *
dowSaturday   1.931e-02  5.273e-03   3.661 0.000251 ***
pm10_laggeg0  3.958e-04  8.997e-05   4.399 1.09e-05 ***
pm10_laggeg1  1.765e-04  9.259e-05   1.907 0.056571 .
pm10_laggeg2 -2.595e-05  9.039e-05  -0.287 0.774090
pm10_laggeg3  1.188e-04  8.350e-05   1.423 0.154770
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
           edf Ref.df Chi.sq p-value
s(temp)  8.396  8.876  161.0  <2e-16 ***
s(time)  7.964  8.720  272.9  <2e-16 ***
s(month) 8.273  8.863  364.5  <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) =  0.262   Deviance explained = 28.3%
UBRE = 0.43535  Scale est. = 1         n = 4362
```

Considerations

- Easy implementation when lags are few; overparametrized when we want to assess a lot of lags
- Collinearity issues: The exposure is likely to be highly correlated with the values of the previous/after days. Weird behaviours in the point estimates (surprising protective effects), variance inflation.

Alternative: to impose some constraints:

- A constant effect within lag intervals
- Average of the exposures in the previous L day
- Describing the coefficients with a smooth curve using continuous functions such as splines, polynomials, and other basis functions.

The idea: β_ℓ can be modelled using a basis function.

Polynomial DLM

Let $\beta_\ell = \sum_j^p \tau_j \ell^j, \quad \ell = 0, \dots, q$, lets write it for 2 lags using a 3rd degree polynomial to see it explicitly:

$$Y_t = \beta_0 + \beta_{10} X_t + \beta_{11} X_{t-1} + \beta_{12} X_{t-2} + \epsilon_t \tag{1}$$
$$\beta_{10} = \tau_0,\ \beta_{11} = \tau_0 + \tau_1 + \tau_2 + \tau_3,\ \beta_{12} = \tau_0 + \tau_1 2 + \tau_2 2^2 + \tau_3 2^3 \tag{2}$$

and we can modify as per first lecture to model more localized structures using: $\beta_\ell = \sum_j^p \tau_j \ell^j + \sum_k^K \nu_k (\ell - \kappa_k)_+^p$, thus:

$$\begin{aligned}
\beta_{10} &= \tau_0 + \nu_1 (0 - \kappa_1)_+^3 + \dots + \nu_K (0 - \kappa_K)_+^3, \\
\beta_{11} &= \tau_0 + \tau_1 + \tau_2 + \tau_3 + \nu_1 (1 - \kappa_1)_+^3 + \dots + \nu_K (1 - \kappa_K)_+^3, \\
\beta_{12} &= \tau_0 + \tau_1 2 + \tau_2 2^2 + \tau_3 2^3 + \nu_1 (2 - \kappa_1)_+^3 + \dots + \nu_K (2 - \kappa_K)_+^3
\end{aligned}$$

and similarly we can penalize it can estimate *the penalised spline distributed lag estimate* of β_ℓ

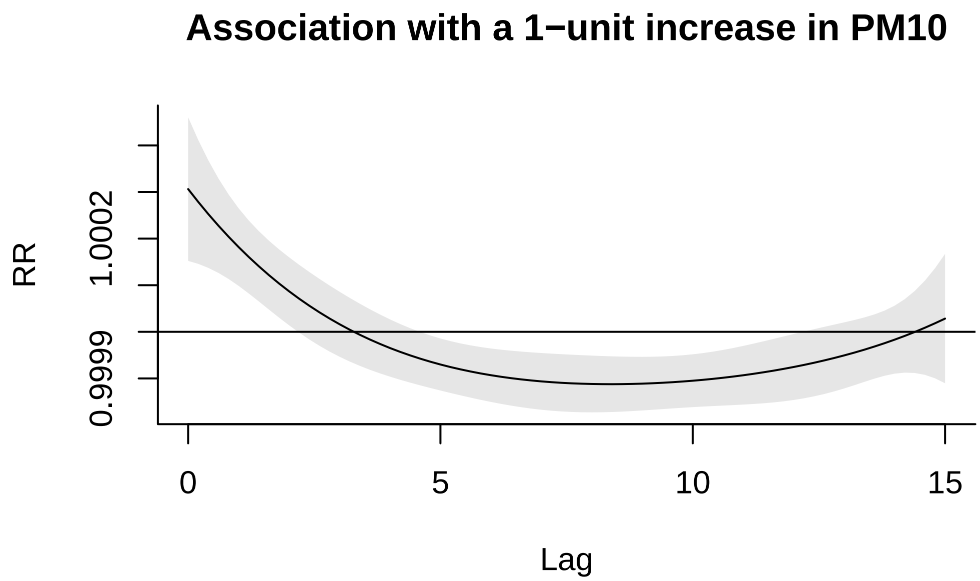
Polynomial DLM in R: Chicago

```
cb1.pm <- crossbasis(chicagoNMMAPS$pm10,
  lag = 15, argvar = list(fun = "lin"),
  arglag = list(fun = "poly", degree = 4)
)

summary(cb1.pm)
```

```
CROSSBASIS FUNCTIONS
observations: 5114
range: -3.049835 to 356.1768
lag period: 0 15
total df:  5

BASIS FOR VAR:
fun: lin
intercept: FALSE

BASIS FOR LAG:
fun: poly
degree: 4
scale: 15
intercept: TRUE
```

Polynomial DLM in R: Chicago

```r
model_dlm <- mgcv::gam(death ~ s(temp) + s(time) + s(month) + dow + cb1.pm,
  family = poisson(), chicagoNMMAPS
)

pred1.pm <- crosspred(cb1.pm, model_dlm, at = 0:20, bylag = 0.2)
plot(pred1.pm,
  ptype = "slices", var = 1, cumul = FALSE, ylab = "RR",
  main = "Association with a 1-unit increase in PM10"
)
```



Polynomial DLM in R: Chicago

```
summary(model_dlm)
```

```
Family: poisson
Link function: log

Formula:
death ~ s(temp) + s(time) + s(month) + dow + cb1.pm

Parametric coefficients:
               Estimate Std. Error z value Pr(>|z|)
(Intercept)   4.734e+00  1.028e-02 460.746  < 2e-16 ***
dowMonday     3.162e-02  5.933e-03   5.330 9.85e-08 ***
dowTuesday    2.100e-02  5.998e-03   3.501 0.000463 ***
dowWednesday  3.579e-03  6.050e-03   0.592 0.554073
dowThursday   3.367e-03  6.069e-03   0.555 0.579092
dowFriday     1.339e-02  6.054e-03   2.212 0.026984 *
dowSaturday   1.805e-02  5.957e-03   3.031 0.002439 **
cb1.pmv1.l1   3.062e-04  7.862e-05   3.895 9.81e-05 ***
```

```
cb1.pmv1.l2  -2.115e-03  1.068e-03  -1.979 0.047789 *
cb1.pmv1.l3   3.966e-03  4.423e-03   0.897 0.369884
cb1.pmv1.l4  -3.477e-03  6.698e-03  -0.519 0.603653
cb1.pmv1.l5   1.348e-03  3.323e-03   0.406 0.684882
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
           edf Ref.df Chi.sq p-value
s(temp)  8.584  8.940  165.0  <2e-16 ***
s(time)  7.658  8.530  261.1  <2e-16 ***
s(month) 8.125  8.806  278.3  <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) =  0.267   Deviance explained = 29.1%
UBRE = 0.4727  Scale est. = 1         n = 3505
```

Polynomial DLM in R: Chicago

Retrieve the cumulative effect. What is the interpretation here?

```
pred1.pm$allRRfit["1"]
```

```
        1 
0.9997512 
```

```
pred1.pm$allRRlow["1"]
```

```
        1 
0.9991884 
```

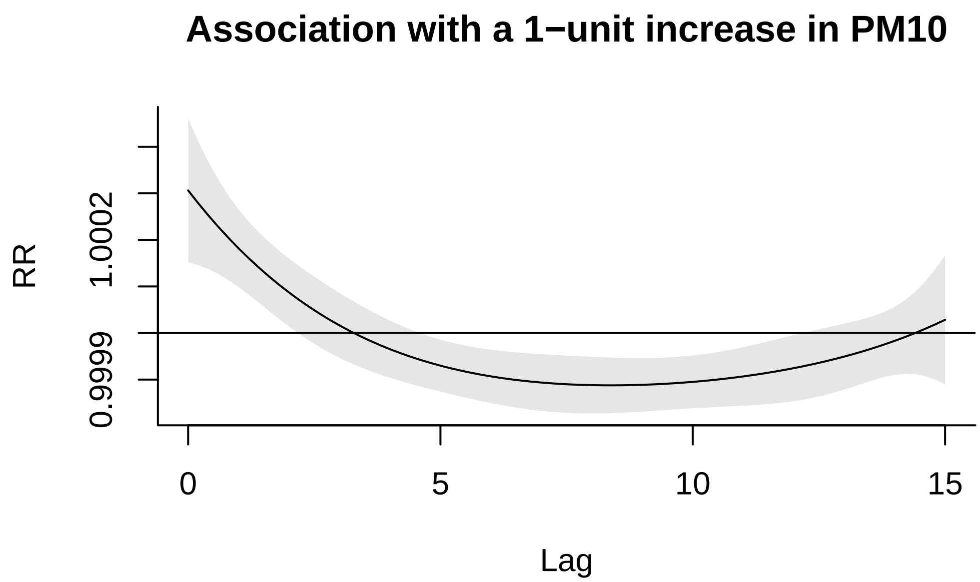
```
pred1.pm$allRRhigh["1"]
```

```
       1 
1.000314 
```

Polynomial DLM in R: Chicago

What is the main assumption here? Can we relax it?

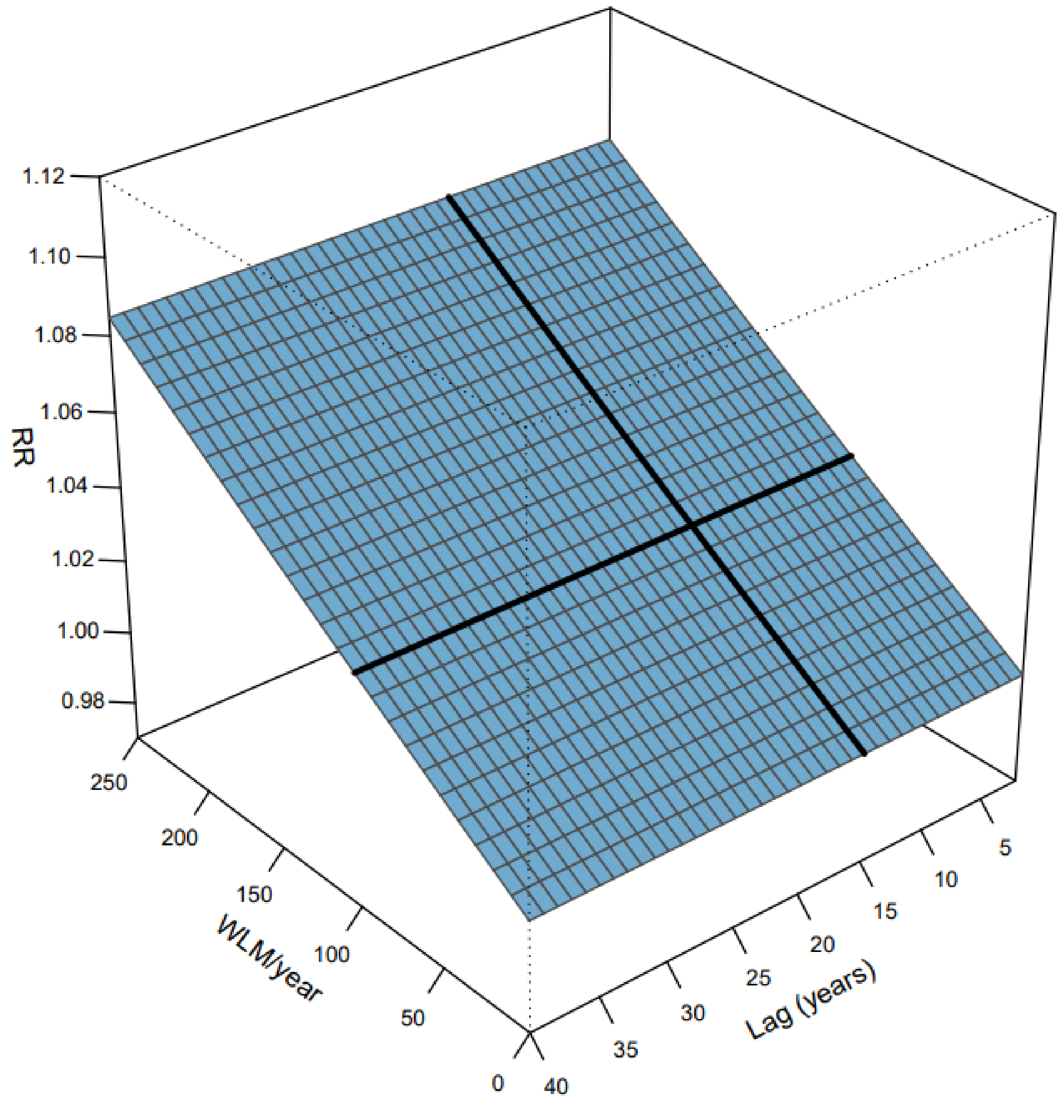
```
plot(pred1.pm,
  ptype = "slices", var = 1,
  cumul = FALSE, ylab = "RR", main = "Association with a 1-unit increase in PM10"
)
```



Extension to distributed non-linear lag models

- We know that temperature and mortality have a U-shape relationship
- We know that high temperature has a lag effect on mortality
- Can we define models to combine these two components?

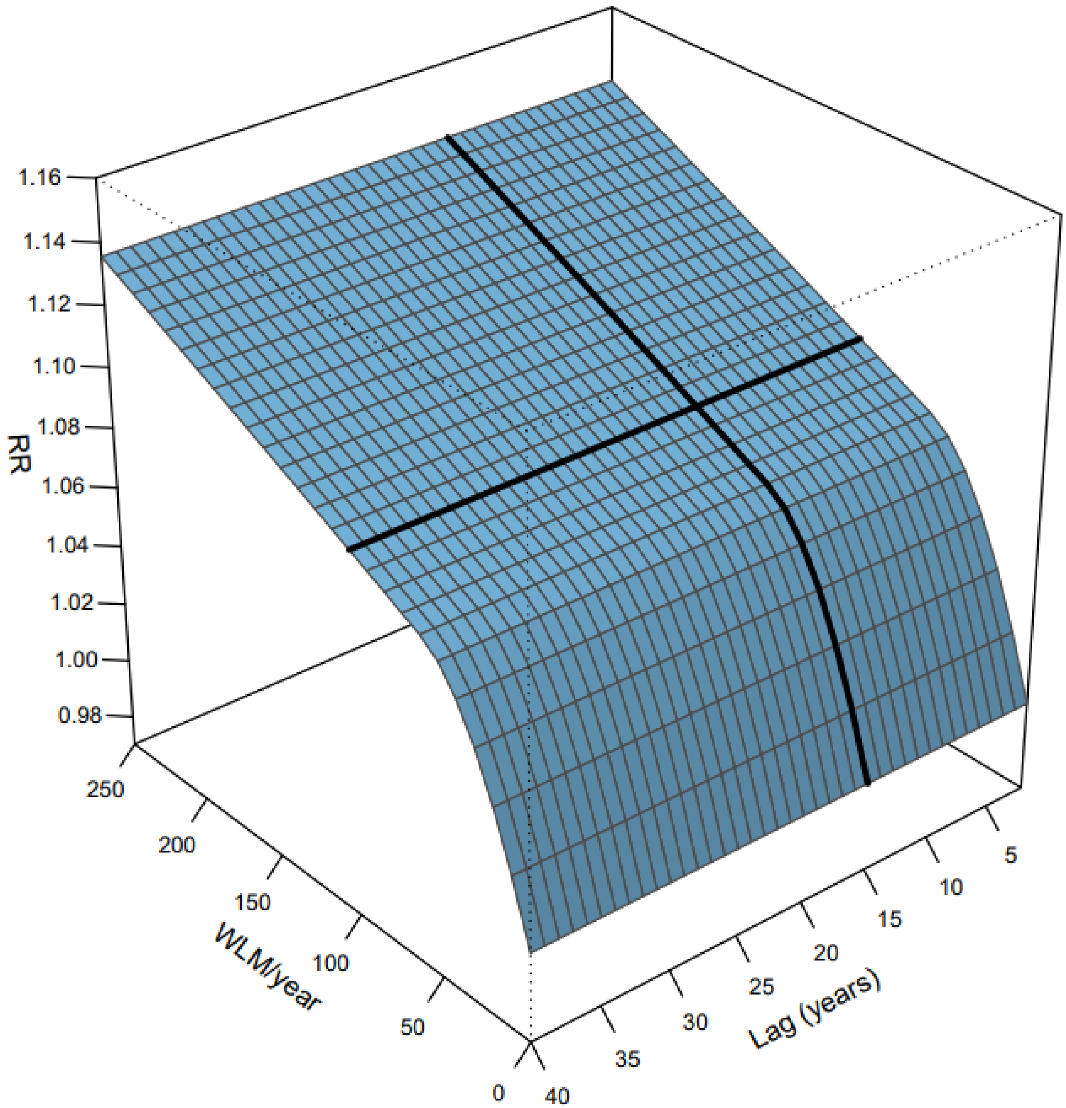
The idea: to calculate this bi-dimensional relationship, we need a basis function that combines the basis function in the lag dimension and the basis function in the exposure dimension: **Cross-basis function**

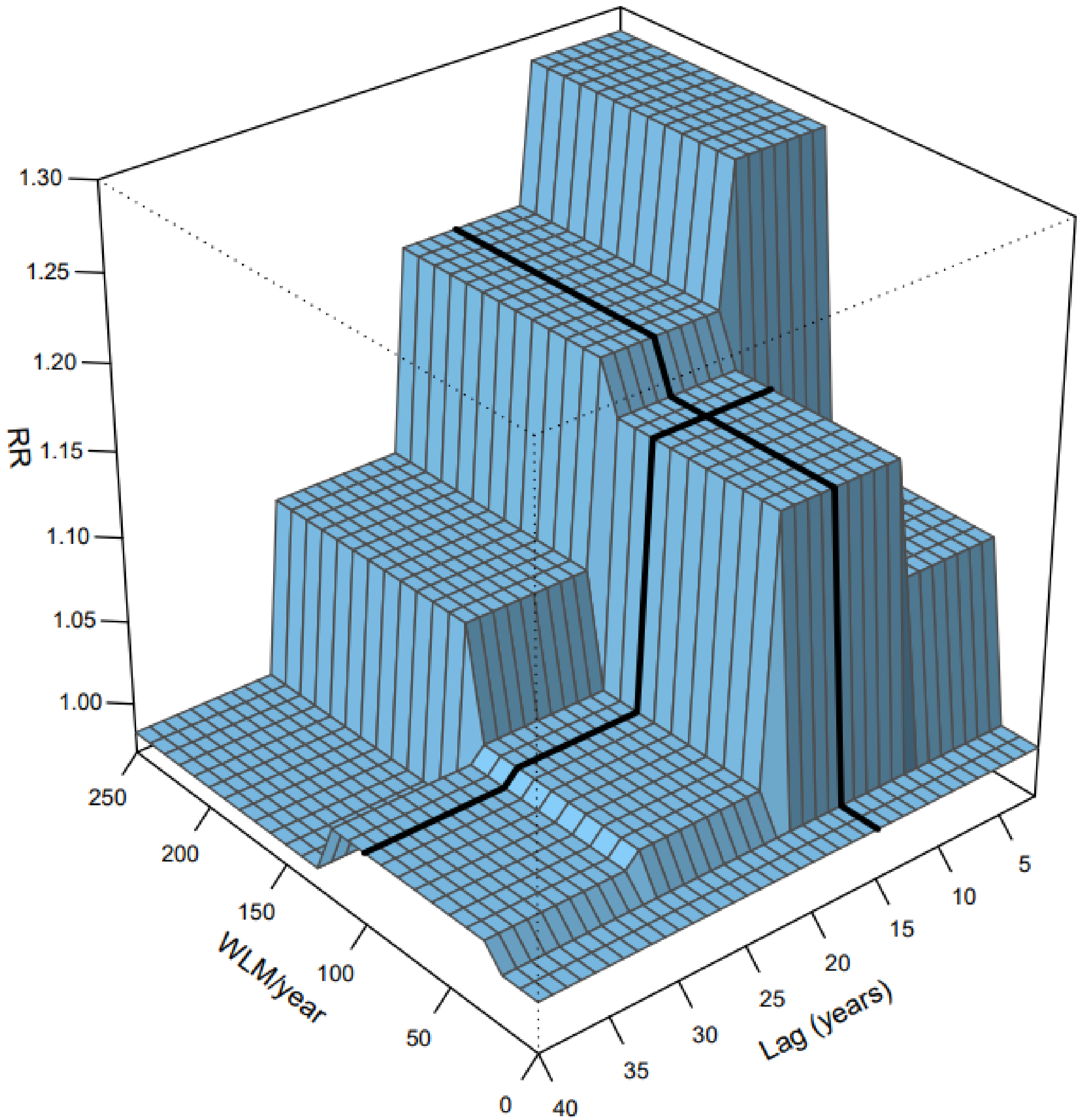


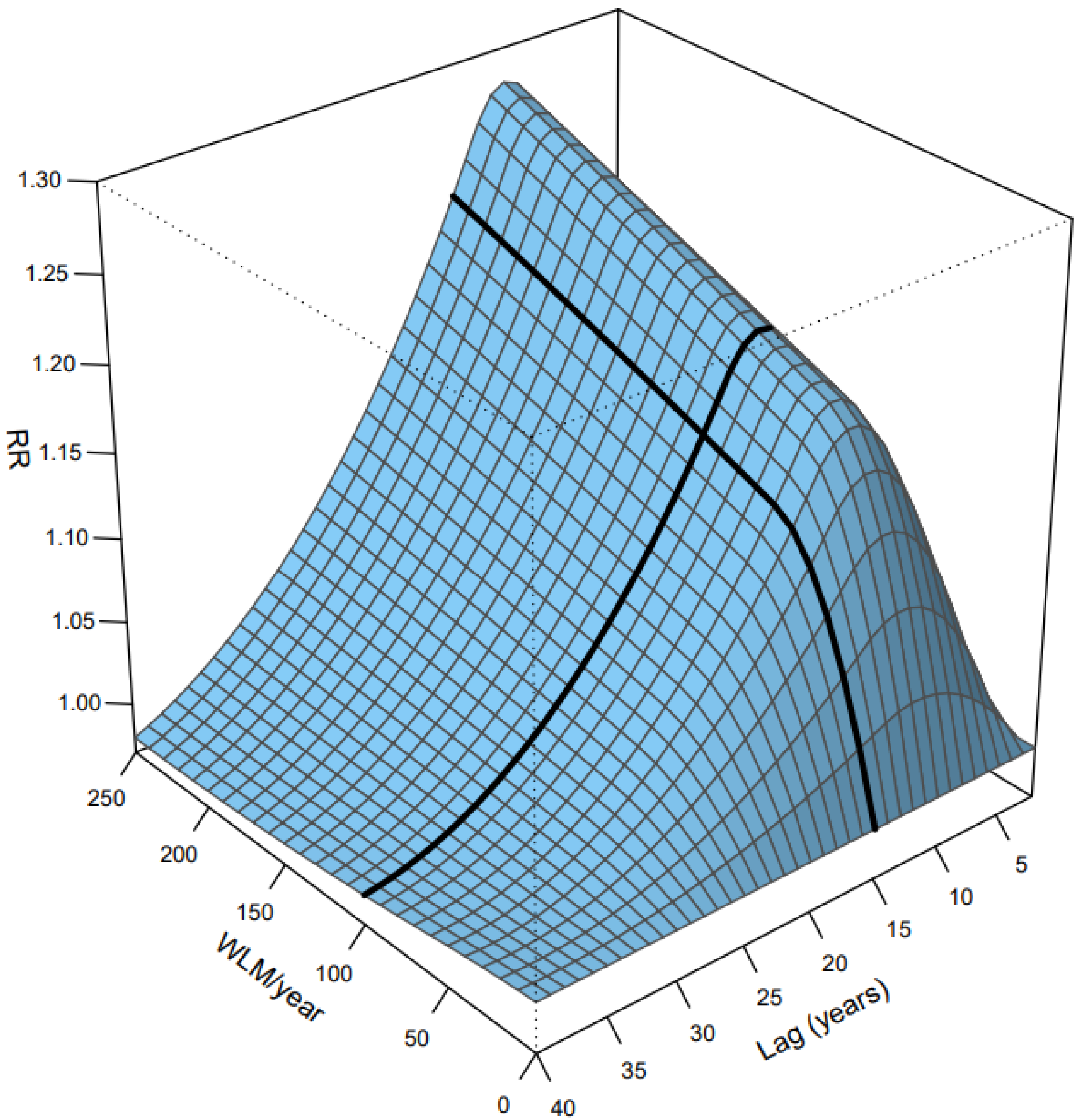
1.12
1.10
1.08
1.06
1.04
1.02
1.00
0.98
RR
250
200
150
100
50
0
WLM/year
40
35
30
25
20
15
10
5
Lag (years)

Linear-by-constant

Spline-by-constant




1.30
1.25
1.20
1.15
1.10
1.05
1.00
RR
250
200
150
100
50
0
WLM/year
40
35
30
25
20
15
10
5
Lag (years)



RR
1.30
1.25
1.20
1.15
1.10
1.05
1.00
250
200
150
100
50
0
WLM/year
40
35
30
25
20
15
10
5
Lag (years)

Step-by-step

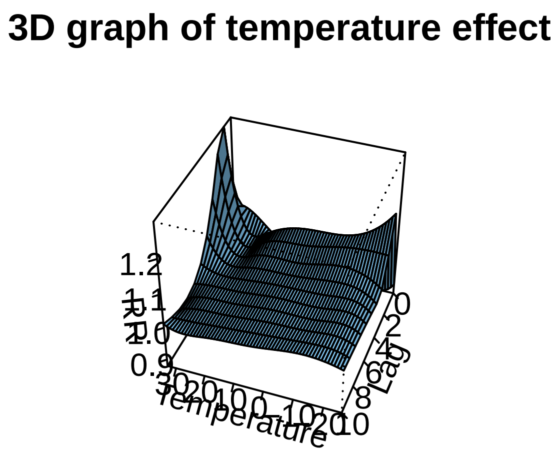
Spline-by-spline

Example 3: Temperature in Chicago

```
cb2.pm <- crossbasis(chicagoNMMAPS$pm10,
  lag = 1, argvar = list(fun = "lin"),
  arglag = list(fun = "strata")
)

varknots <- equalknots(chicagoNMMAPS$temp, fun = "bs", df = 5, degree = 2)
lagknots <- logknots(10, 3)
cb2.temp <- crossbasis(chicagoNMMAPS$temp, lag = 10, argvar = list(
  fun = "bs",
  knots = varknots
), arglag = list(knots = lagknots))


model_dlm2 <- mgcv::gam(death ~ cb2.pm + cb2.temp + s(time) + s(month) + dow,
  family = poisson(), chicagoNMMAPS
)

pred2.temp <- crosspred(cb2.temp, model_dlm2, cen = 21, by = 1)
```

Example 3: Temperature in Chicago

```
plot(pred2.temp,
  xlab = "Temperature", zlab = "RR", theta = 200, phi = 40, lphi = 100,
  main = "3D graph of temperature effect"
)
```

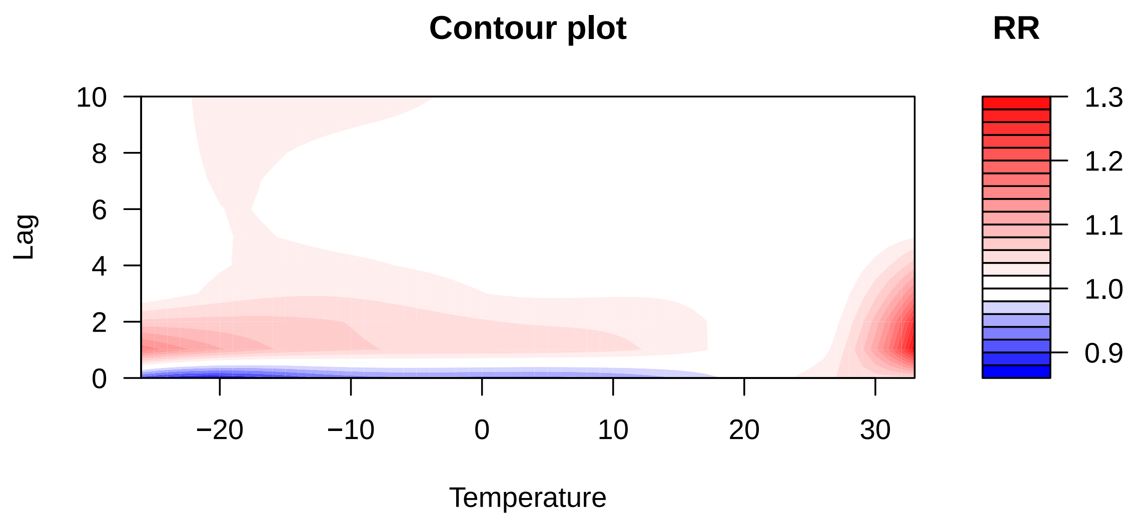


Example 3: Temperature in Chicago

```
library(plotly)
p <- plot_ly()
p <- add_surface(p, x = 0:10, y = -20:30, z = pred2.temp$matRRfit)

layout(p, scene = list(
  xaxis = list(title = "Lag"),
  yaxis = list(title = "Temperature", range = c(0, 30)),
  zaxis = list(title = "Relative risk")
))
```

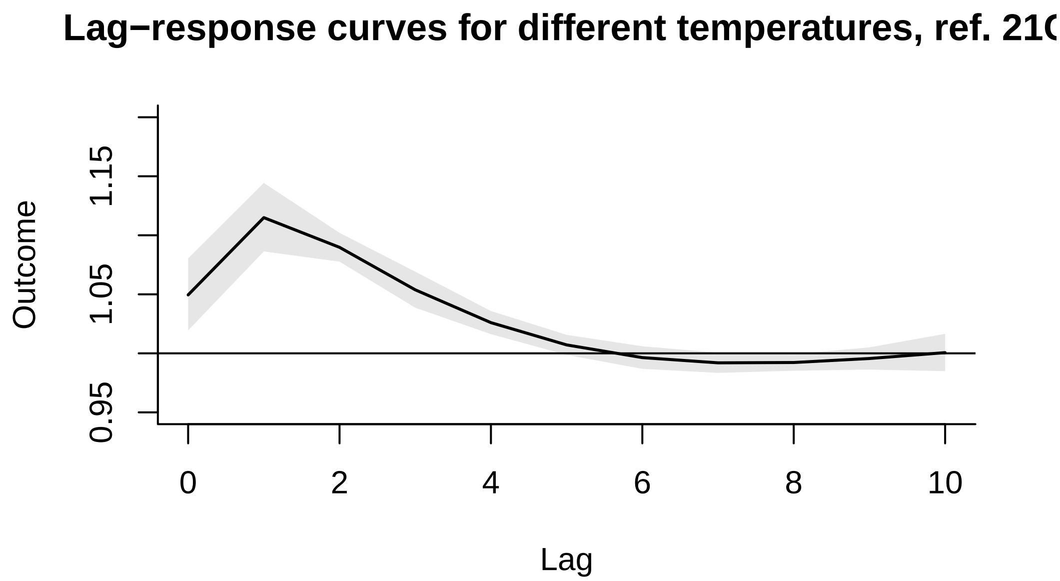
Example 3: Temperature in Chicago

```
plot(pred2.temp, "contour",
  xlab = "Temperature", key.title = title("RR"),
  plot.title = title("Contour plot", xlab = "Temperature", ylab = "Lag")
)
```



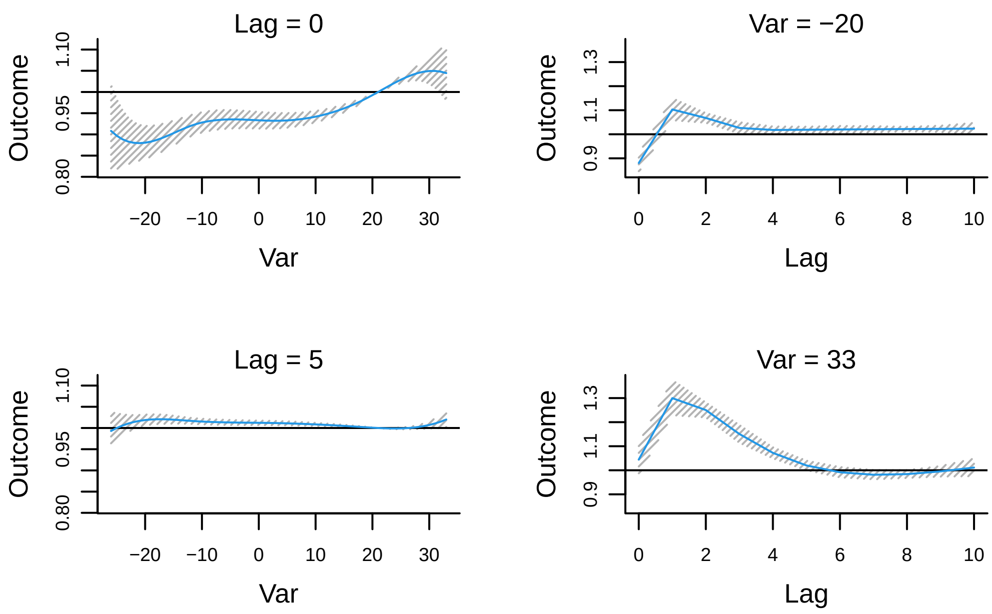
Example 3: Temperature in Chicago

```
plot(pred2.temp, "slices",
  var = 30, col = 1, ylim = c(0.95, 1.2), lwd = 1.5,
  main = "Lag-response curves for different temperatures, ref. 21C"
)
```



Example 3: Temperature in Chicago

```
plot(pred2.temp, "slices",
  var = c(-20, 33), lag = c(0, 5), col = 4,
  ci.arg = list(density = 40, col = grey(0.7))
)
```



Summary

- Extend basis function to incorporate the different lags
- Distributed lag linear models
- Distributed lag non-linear models
- Can we expand to space?

Check : https://cran.r-project.org/web/packages/dlnm/ vignettes/dlnmTS.pdf

Questions?